



Europäisches Patentamt
European Patent Office
Office pour le dépôt des brevets

(11) Veröffentlichungsnummer:

0 148 426
A3

(12)

EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: 84114893.5

(51) Int. Cl. 4: B 65 D 51/00

(22) Anmeldetag: 07.12.84

(30) Priorität: 22.12.83 DE 3346351

(43) Veröffentlichungstag der Anmeldung:
17.07.85 Patentblatt 85/29

(88) Veröffentlichungstag des später
veröffentlichten Recherchenberichts: 21.08.85

(84) Benannte Vertragsstaaten:
AT BE CH DE FR GB IT LI LU NL SE

(71) Anmelder: Pharma Gummi Wimmer West GmbH
Stolberger Strasse 21-27
D-5180 Eschweiler(DE)

(72) Erfinder: Wimmer, Hans
An Adamshäuschen 13
D-5100 Aachen(DE)

(74) Vertreter: Patentanwälte Dipl.-Ing. Hans Schmitt
Dipl.-Ing. Wolfgang Maucher
Dreikönigstrasse 13
D-7800 Freiburg i.Br.(DE)

(54) Pharmazeutischer Stopfen, Kolben od. dgl. und Verfahren zum Herstellen von pharmazeutischen Stopfen, Kolben od.
dgl.

(57) Bei einem pharmazeutischen Stopfen (2), Kolben od. dgl. dgl. den Behälter (1) gas-, wasserdampfdicht usw. abschließt
Gummiteil zum Verschließen einer Medikamentenflasche (Fig. 1).

(1), Unterteilen eines Spritzenzylinders od. dgl. besitzt der
Stopfen, Kolben od. dgl. Verschlußteil eine gegenüber dem Inertfilm (8) und dem gummielastischen Teil des Stopfens im
Behälterinhalt (12) weitgehend inerte Schicht. Dazu sind am Bereich einer Durchstichstelle für einen Infusionsdorn unter-
im wesentlichen zylindrischen Hals (4) des Stopfens (2), brochen sein.

Kolbens od. dgl. an einem dementsprechenden Behälterin-
nenraum (6) zugewandten, mindestens teilweise an der
Behälterinnenwand (7) oder dessen Mündung anliegenden
Bereich ein fluorierter Polymerfilm (8) od. dgl. Inertfilm
vorgesehen und ein weiterer Bereich des Stopfenhalses (4)
liegt unmittelbar an der mindestens im wesentlichen zylin-
drischen Wand der Behältermündung an.

Beim Herstellungsverfahren für den Stopfen od. dgl.
sind drei Arbeitsschritte vorgesehen: Ein zuerst herzustellen-
des Stopfenteil wird zusammen mit einem fluorierten Poly-
merfilm (8) od. dgl. gleichzeitig hergestellt, unter mindestens
teilweiser Vulkanisation dieses Stopfenteiles, dieses Zwi-
schenprodukt wird ausgestanzt und in ein zweites Formwerk-
zeug eingebracht und in einem dritten Arbeitsschritt werden
ein Stopfenaußenteil mit dem vorerwähnten Stopfeninnen-
teil zusammengefügt und ausvulkanisiert. Der dem Behälte-
rinhalt zugewandte fluorierte Polymerfilm (8) od. dgl. geht
praktisch keinerlei Reaktion mit diesem ein, während ein
äußerer, gummielastischer Teil des Stopfenhalses (4) od.

A3
0 148 426 EP

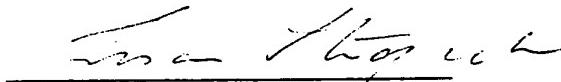
/...

THE PATENTS ACT 1977

IN THE MATTER OF
European Patent (UK)
No. 84 114 893.5
of 

I, Susan Högerich of Josef-Schmid-Strasse 19, D-7619 Steinach, Federal Republic of Germany, hereby declare that I am conversant with the German and English languages and that to the best of my knowledge and belief the attached document is a true and correct translation made by me of the original text of European Patent No. 84 114 893.5 in name of Pharma-Gummi Wimmer West GmbH.

Signed this 18th day of December 1988



The invention relates to a method for producing a pharmaceutical stopper, piston or similar seal which consists essentially of rubber or a similar elastomeric material and serves to close or subdivide a bottle, a barrel of a syringe, or a similar container, the stopper, piston or the like having in a sealing area facing the interior of the container a coating of a fluorinated polymer film or similar inert film only partly surrounding said sealing area of the stopper at the side thereof facing the wall of the container opening, so that a further part of the uncoated sealing area of the stopper sealingly butts against the container opening. The invention also relates to a pharmaceutical stopper, piston or similar rubber seal for closing or subdividing a bottle, a barrel of a syringe or a similar container.

Stoppers of different shapes and materials are implemented to seal and close medicine bottles (cf. e.g. DE-A-19 01 239, DE-A-19 46 566).

Such stoppers often consist of natural or synthetic rubber, rubber-elastic or pure thermoplastics. It is precisely the elastic properties of such materials which permit the relative stoppers to make up for the tolerances of bottle openings or of barrels or syringes and enables them to seal a container or the like well, even over a lengthy period.

However the pharmaceutical preparations - as a rule in liquid or powdery form - to be stored in a closed state in glass bottles, barrels of syringes or similar containers make very different demands on the material to be used for the stopper. Thus, for example, a rubber stopper has to be biologically or chemically compatible with the contents of the bottle. In addition, it is important that the closing stopper be impermeable to gas or water vapour when the contents of the bottle are sensitive to oxygen or moisture. Furthermore, the material of the stopper must not give rise to any change in the therapeutic value of the contents of the container, e.g. by giving off harmful components or ones changing a pharmaceutical medicament or by absorbing constituents from the pharmaceutical preparation or the like. A great many compositions of materials for stoppers are capable of only partly solving the above-mentioned problems.

Therefore a stopper-like closure has already been produced which sealingly engages with a ring-shaped web into the bottle-neck of a container (DE-A-32 31 179). This prior art closure has above its web a plate-like and outwardly disposed cap resting upon the bottle opening. In order to seal the container well, the cap of the prior art closure is fitted firmly on the bottle opening with a metal closure or top engaging behind a flanging of the bottle opening.

The ring-shaped web contacting the contents of the container is surrounded by a layer consisting of an inert fluorocarbon resin applied to this area of the closure by, for example, vulcanization. This inert layer is dimensioned so as also to cover the flanging of the bottle opening.

Such layers of chemically highly inert and resistant polymers can indeed largely eliminate the problem of incompatibility between material of the stopper on the one hand and contents of the container on the other hand. However, the high-grade foil material required for producing the layers is very expensive. This has negative repercussions, particularly for such closures where the lower side thereof impacting the bottle opening and contacting the contents of the container is almost completely coated with such an inert layer.

Above all, the foils forming the inert layer in stoppers are of considerable hardness and of limited deformability, so that the desired, dependable sealing between the glass container or the like on the one hand and the stopper provided with a fluorinated polymer foil on the other hand is not produced when the polymer foil sheathes the entire stopper neck to be inserted into the container opening, into the barrel of a hypodermic ampoule or the like. Although the relatively hard polymer film of limited elasticity impacting the glass is capable of sealing against liquids, it cannot prevent the penetration of gases and bacteria. The permeability to gas and water vapour at the boundary surface between the fluorinated foil of the stopper neck on the one hand and the inside wall of the container on the other hand can become so high that, for example, a vacuum within a container cannot be maintained over sufficiently long periods. Therefore, for example, the above-described, prior art stopper-like closure has a concentric projection which is disposed in the outer edge area of that side of the closure cap impacting the bottle opening and is kept free of the inert layer, the projection sealing an internally evacuated container against, e.g. the entry of ambient air at least for the time between the capsulation and the ensuing

closure by means of the metal closure or top. Such a vacuum is necessary, for example, for a large number of freeze-dried products.

Through the contact of two hard substances - such as the fluorinated polymer film on glass - the sterility necessary for medicinal containers cannot be ensured over lengthy periods. If, as for example DE-A-21 46 421 and DE-A-32 31 179 show, only a narrow portion of the flange-like cap of a rubber-elastic closure covers an end face of a container, sufficient sealing against permeability to gas and water vapour is no longer constituted with the necessary degree of certainty.

Also it is regularly hardly possible to prevent folding and pores when producing the above-mentioned stoppers provided with a fluorinated polymer foil, particularly when these foils have to undergo considerable deformation. The folding then leads to new problems with respect to the sealing between glass and closing stopper; the pores permit unwanted contact between the contents of the container and the rubber stopper.

One has also already produced a stopper of rubber-elastic material, a protective cap which is made of resistant material and is adapted in shape being placed on the stopper over its sealing area projecting into the interior of the container and being held there mechanically. This protective cap is dimensioned such that a further part of the uncoated sealing area of the stopper butts sealingly against the container opening (GB-A-1 061 810). The cap and the rubber-elastic stopper part are there hence not inseparably connected by vulcanization.

Through the protective cap being mechanically placed later, this not only makes the method of producing this prior art stopper more laborious, but also involves the danger of the protective cap being sucked into the container when the latter is under vacuum - as for example in the case of freeze-dried products. In order to be able to assemble the prior art stopper together with the protective cap, the stopper has to have a certain minimum wall thickness which, with inert, regularly brittle materials, leads in turn to poor sealing. Through the mechanical assembly of elastomer and inert stopper part, the sterility often required, for example for medicinal preparations, can also hardly be maintained during use of the stopper, particularly at the joints.

Vulcanizing the rubber-elastic material of the stopper onto an inert film can however lead in the production process to rubber-elastic material flowing past the outer edge of the cap-like inert film, wetting and contaminating the inert film on the side thereof later facing the interior of the container, and thwarting its original, intended function, namely, the chemical neutrality of the stopper.

It follows from all the foregoing that one has long since sought a method and a corresponding stopper or similar seal in which it is possible to simultaneously combine on the one hand the advantageous properties of elastomers, the elastic behaviour thereof and good sealing even on the uneven area of, for example, the openings of glass containers and on the other hand the advantageous properties of inert plastics, namely, the chemical neutrality thereof, without having to put up with the respective disadvantages of such materials to an appreciable extent.

The object underlying the invention is therefore to devise a method of favourable expense for producing stoppers, pistons or similar seals which present good sealing against liquid, gases and water vapour as well as against the penetration of germs etc. The chemically inert constituent of the stopper, piston or similar seal is to be applied in the method in such a way as to dependably avoid any interaction between the material of the stopper or the like on the one hand and the contents of the container on the other hand, for example by subsequent impurities of by the inert material becoming unintentionally detached.

At the same time it is also the object to devise a stopper, piston or similar seal which lends itself to sealing well, even at uneven surfaces of the container, and is largely neutral in behaviour relative to the contents of the container.

The object is accomplished according to the invention in the method of the kind mentioned at the outset in that the stopper or the like is produced in several working steps, in the first step an unvulcanized rubber sheet together with a fluorinated polymer film or similar inert film is initially pressed into a calibre plate of a first moulding tool and then corresponding portions of the polymer film or the like and of the rubber sheet assume the outer contour corresponding to the hollow mould(s) provided in the calibre plate, polymer film or the like resting against the wall of the hollow mould being inseparably connected under the influence of heat to the part of the rubber sheet lying within and being vulcanized to form in each case one inner sealing part of the stopper, that in the next working step the

inner sealing parts of the stopper which have thus been formed and are coated with the fluorinated polymer or the like are removed from the first moulding tool and in the next working step are punched out of the coated rubber sheet in such a manner that the upper edge of each inner rubber sealing part protrudes somewhat radially with a diameter beyond the diameter given by the hollow mould, that in the next working step in which the inner sealing part is placed in the hollow mould(s) of a second moulding tool this protruding upper edge upwardly seals these hollow mould(s) in such a way as to prevent that in the next working step, when the inner sealing part is joined to an outer part of the stopper, unvulcanized rubber material of the subsequent outer part of the stopper enters the area between fluorinated polymer film or the like and the wall of the hollow mould of the second tool.

The method according to the invention makes it possible not only to undetachably apply inert foil material also to only a partial area of the sealing area belonging to a stopper and projecting e.g. into a bottle neck, but also to largely avoid that initially not yet vulcanized, elastic stopper material completing the stopper or the like in a further working step moves into the region of the inert foil material and there may then be an unwanted interaction between the elastic stopper material on the one hand and the contents of the container on the other hand. Accordingly one obtains a stopper or the like with which the contents of the container can establish contact practically only with the fluorinated polymer film or similar chemically inert film part of the stopper, while a further part of the stopper neck or the like with its rubber-elastic material against the

inside wall of the container provides good sealing against liquids, gases, water vapour as well as sealing against the penetration of germs through direct contact of rubber stopper and container glass or the like. The advantages of hitherto known materials for closures are combined in the region of the stopper neck or the like, without one having to put up with their respective disadvantages. The polymer film or the like, which from the point of view of material is expensive, extends only over a relatively small part of the entire stopper which can therefore be produced comparatively inexpensively. In addition, a stopper composed of three layers, for example, can also be realized in the method according to the invention, the coating which is always thin and saves material covering a stopper area which is essentially exactly defined geometrically. "Layer" and "layer of material" are here understood to be in particular stopper portions disposed adjacent to one another in the axial direction, for example the inert foil material as the "first layer", the elastomeric material undetachably connected thereto as the "second layer" and the further elastomeric material which is to be applied to the latter elastomeric material in a last method step of the invention and forms the outer part of the stopper as the "third layer". A stopper composed of three layers is to be understood along these lines, particularly if - as is to be set forth in closer detail - the outer elastomeric layer of material has a different composition than the elastomeric layer of material which is undetachably connected to the inert foil layer. The stopper or the like produced in the method according to the invention is capable of behaving largely neutrally with respect to the contents of the container owing to the inert foil layer. However the stopper moreover has the special advantage

that through this layer being undetachably connected to the elastomeric stopper material, no impurities can lodge in the joint region of these layers and therefore the required sterility of the stopper or the like can be fulfilled in a simple way. In the method according to the invention the inner stopper part to be provided with a chemically inert film is produced in separate production steps. The rubber sheet onto which, for example, the chemically inert film was laminated beforehand, is put into the production mould in the form of initially a flat compound or individually, and is there deformed by pressure and heat into the envisaged shape and is at the same time inseparably connected. In this deforming process, the rubber material acts as a kind of elastic pressure pad serving to bring the foil into the desired final shape under the temperature and pressure conditions prevailing in the mould. Formation of folds and pores is thereby largely avoided as the foil is deep drawn.

Additional further developments of the method according to the invention are recited in the sub-claims relating to the method and in the specification. The method according to claim 4 relates to a deep drawing operation which is devised to be particularly careful in treatment.

Since the inert foil is not mechanically connected to the elastomeric material in the method according to the invention, very thin layers of material, e.g. of the comparatively expensive fluorinated polymer film or the like, can also be used.

Claim 6 describes a method of producing a stopper or similar seal which can be fixed especially well, e.g. in the neck of a bottle. Claim 7 is concerned with a stopper or similar seal which, through being composed of three layers, enables the properties of the material in the individual stopper areas to be optimized further.

As already mentioned, the invention also relates to a pharmaceutical stopper, piston or similar rubber seal for closing or subdividing a bottle, a barrel of a syringe or a similar container. In such a pharmaceutical stopper or the like according to the present invention, a stopper area facing the interior of the container is partly coated with and inseparably connected by vulcanization to a fluorinated polymer film or the like, only one portion of the stopper shaft or the like being covered by the fluorinated polymer film or the like and a further part of the essentially cylindrical sealing portion as well as a stopper part averted from the interior of the container having a sealing face free of coating.

Such a pharmaceutical stopper leads to the advantages as were also discussed above in connection with the stopper produced according to the method, particularly also in comparison with the stopper according to GB-A- 1 061 810.

Further developments of advantage in this method for producing pharmaceutical stoppers, pistons or similar seals are recited in sub-claims 2 to 9, further developments of advantage in the stopper, piston or similar seals according to claim 10 are recited in sub-claims 11 to 17.

The invention is described more closely below in connection with the figures and with reference to exemplified embodiments of advantage. The drawings show in

Fig. 1 a longitudinal section through a medicine bottle closed by a stopper,

Fig. 2 a side view, partly in section, of a stopper similar to that of Fig. 1,

Fig. 3 a partial longitudinal section of an open production mould for the stoppers,

Fig. 4 a partial section of the closed production mould corresponding to Fig. 3,

Figs. 5a the inner parts of the stopper which are punched out of a and 5b first "rubber sheet",

Fig. 6 the second production mould for a stopper, the mould being in the open position and in partial longitudinal section,

Fig. 7 a partial longitudinal section of a final production mould similar to Fig. 6,

Fig. 8 a partial longitudinal section through a stopper which has been produced according to Fig. 7 and is inside a bottle opening.

Fig. 9 a longitudinal section through a stopper which is in the top of a medicine bottle and through which an infusion prick is passed,

Fig. 10 a longitudinal section through a stopper corresponding to Fig. 9, from which the infusion prick has been withdrawn,

Figs. 11a lower parts of stoppers similar to Figs. 5a and 5b and 11b wherein the connecting surface between the fluorinated polymer film and the rubber-elastic part of the stopper is interrupted in the puncture area for an infusion prick,

Fig. 12 a partial longitudinal section of an open production mould for the lower part of the stopper according to Fig. 11a,

Fig. 13 a partial longitudinal section of an open production mould for the stoppers similar to Fig. 3, however for a somewhat modified mode of production,

Fig. 14 a partial longitudinal section of the production mould according to Fig. 13 in the closed condition,

Fig. 15 a side view, partly in section, of a stopper similar to that of Fig. 2, the rubber-elastic part thereof consisting of two different materials,

Fig. 16 a side view, partly in section, of a freeze-drying stopper,

Fig. 17 a side view, partly in section, of a twin chamber hypodermic ampoule in which there are a piston as the closure of the barrel and a further piston as the subdivision of the barrel of the syringe and
in

Fig. 18 a side view, partly in section, of a piston for a hypodermic ampoule.

Fig. 1 shows a medicine bottle 1 closed by a pharmaceutical stopper which is designated altogether by 2 and will also be referred to in short as "stopper 2" in the following. The latter is devised to be a shaped stopper and has in a known manner a stopper neck 4 inserted in the bottle opening 3 and an outer part radially protruding beyond said neck in a flange-like manner. It forms part of the invention that this stopper 2 according to the invention is partly coated with a fluorinated polymer film or the like at an area of the stopper facing the interior 6 of the container and is inseparably connected thereto by vulcanization, however only one portion (cf. for example portion 30 in Fig. 16 and portion 34 in Fig. 13) of the stopper shaft or the like being covered by the fluorinated polymer film 8 or the like and a further part 14; 29 (cf. Fig. 2 and Fig. 16, respectively) of the essentially cylindrical seal portion as well as a stopper part 5 or 5' averted from the interior 6; 20, 21 of the container having a sealing surface free of coating. "Container wall" is here understood to be not only the inside wall 7 of the interior of the medicine bottle 1 according to Fig. 1, but especially the wall 100 which belongs to the bottle opening and receives the stopper neck 4 and e.g. in the configuration according to Fig. 17 the inside wall of the barrel 22 of the hypodermic ampoule 16.

With regard to the modified embodiments of the stopper 2, reference is made particularly to the description below of Figs. 16 to 18.

Preferably the following fluorinated high polymers come into question as fluorinated polymer films or the like:

polytetrafluoroethylene (PTFE)
tetrafluoroethylene-perfluoropropylene copolymer (FEP)
perfluoroalkoxy copolymer (PFA)
ethylene-tetrafluoroethylene copolymer (ETFE)
polyvinylidene fluoride (PVDF)
polyvinyl fluoride (PVF)

Although these are the preferred materials for the fluorinated polymer film 3, the same may also consist of other materials which on the one hand are inert and biologically compatible with respect to the contents 12 of the container and on the other hand are capable of being anchored firmly enough to the neighbouring area of the rubber-elastic part of the stopper 2, possibly with the interposition of adhesive agents. Such materials are also referred to in short as "inert film" in the application. The rubber-elastic part 9 of the stopper 2 may consist essentially of natural or synthetic rubber, rubber-elastic or pure thermoplastics. These materials are here called in short "rubber", the stopper consisting thereof is called in short "rubber stopper" and the stopper parts consisting of these materials are called "rubber-elastic parts".

Fig. 2 shows a stopper 2a similar to the stopper according to Fig. 1. It is readily evident that in this shaped stopper 2a the fluorinated polymer film 3 extends up to a little above a conical insertion part 13 of the stopper neck 40. The medicine bottle 1 is sealed by pressing the cylindrical part 14 of the stopper neck 40 into the bottle opening 3. This sealing serving particularly against the penetration of gas, water vapour, bacteria etc. can be further increased in that the underside 15 of the stopper top

5 protruding in a flange-like manner is pressed onto the end face 10 of the bottle opening 3, this for example in practice usually being done with suitable flanged caps.

Figs. 1 and 2 show well that in practice the contents 12 of the container cannot come to react with the rubber-elastic part of the stopper 2a, even under unfavourable circumstances, but that this part assumes a function of sealing the interior 6 of the container relative to the environment, the relatively hard, fluorinated polymer film 3 being unable to assume said sealing function relative to the usually uneven inside wall 7 of the container.

It also becomes clear from Figs. 1 and 2 that the inert film 3 forms on the rubber-elastic part 9 a thin coating which is geometrically more or less exactly defined. This is rendered possible by the method according to the invention by being able to inexpensively produce e.g. the stoppers shown in Figs. 1 and 2, which simultaneously combine on the one hand the advantageous properties of elastomers, the elastic behaviour thereof and good sealing also on uneven bearing surfaces and on the other hand the advantageous properties of inert plastics, namely the chemical neutrality thereof, without having to put up with the respective disadvantages of such materials to an appreciable extent.

The method of production according to the invention proceeds as follows:

For the stopper part 40 (cf. Fig. 2) to be produced first, there is a first moulding plate 41 (cf. Fig. 3) which together with a first counter-plate 42 composes the first moulding tool 45 for the first working step. This moulding tool is shown in schematic form and in the open position in the partial longitudinal section of Fig. 3.

The stopper part to be produced first is designated by 40 in Fig. 2 and is indicated schematically by a dash-and-dot line 44 as being separate from the second stopper part 43 to be additionally produced. This dash-and-dot line 44 may also coincide with the plane separating the different materials 33 and 39 of the stopper (cf. Fig. 15).

In the embodiment according to Fig. 2, the separating plane is selected in consideration of the bowl-shape of the polymer foil 3, with a view to a suitable possibility for production.

An unvulcanized "rubber sheet 46" and an undefomed, flat polymer foil 3a, shown in schematic form, are disposed between the opened parts 41, 42 of the first tool designated altogether by 45. In the pertinent professional circles one understands by "rubber sheet" a rubber layer of a certain expanse in length and width, with which a mould can usually be covered at the edges so far as to permit a working step. The foil-like fluorinated polymer film 3a initially still in a flat state, in accordance with Fig. 3, may already be firmly connected to the rubber sheet 46 in this production stage or, as shown in schematic form in Fig. 3, it may be placed between the mould parts 41 and 42 independently of and in spaced relationship to the rubber sheet 46. Connecting the fluorinated polymer film 3a to the unvulcanized rubber sheet 46 has the advantage, among others, of it being simpler to place the parts 46, 3a between the first moulding plate 41 and the first counter-plate 42. Placing rubber sheet 46 and flat, fluorinated polymer film 3a (Fig. 3) separately has the advantage, among others, of it being possible to save a special working step for connecting rubber sheet 46 and fluorinated polymer film 3a.

Fig. 4 shows the first moulding tool of Fig. 3 in the closed position. Here the initially unvulcanized rubber sheet now

designated by 46a has been pressed into the hollow moulds 47 corresponding to the stopper part 40 to be produced first. In so doing, the fluorinated, initially flat polymer film 3a has been given the desired bowl-shape and in Fig. 4 is designated by "3". When the first moulding tool 45 (Fig. 4) is closed under pressure, the unvulcanized rubber sheet material together with the fluorinated polymer film 3a is pressed into the hollow mould 47 (=calibre mould 47). The fluorinated polymer film 3 or the like is thereby deep drawn, as is readily evident in Fig. 4. It is an important aspect of the invention that the associated rubber material of the rubber sheet 46 or 46a acts as an elastic pressure pad on this fluorinated polymer film 3 or the like.

It is appropriate if the first moulding plate 41 may already have a raised temperature (approx. 120°C to 210°C, preferably 150°C to 190°C) and one can allow the pressure arising in the calibre moulds 47 to increase slowly. The deep drawing process of the fluorinated polymer film from a flat shape 8a according to Fig. 3 into the bowl-like shape of Fig. 4 can consequently be conducted with care, the material of the rubber sheet also acting in a favourable manner as an elastic pressure pad.

As and/or after the first moulding tool is closed, the unvulcanized rubber sheet 46 or 46a is vulcanized on through the influence of temperature. Depending on the pre-treatment of the fluorinated polymer film 3a, 3 or the like, the latter is then physically or chemically inseparably connected to the rubber-elastic part of the later stopper, as a rule by vulcanization on the entire common connecting surface. After this process has been concluded, the vulcanized rubber sheet 46a, having on one side thereof the fluorinated polymer film 3, is removed from the first moulding

tool 45 and the stopper parts 40 first produced in this manner are punched out. The latter are punched out in such a way that when the stopper parts 40 first produced are placed in the second moulding tool 48 (cf. Fig. 6), the stopper part 40 first produced ensures sealing against material of the second rubber sheet 50 (Fig. 6) flowing past the finished stopper part 40 coated with fluorinated polymer into the associated calibre moulds 47a of the lower calibre plate 49 of the second moulding tool.

This is achieved by sealing through the upper edge 52 when this stopper part 40 first produced is inserted into the lower calibre plate 49 of the second moulding tool; by way of example through the diameter D 3 of the hollow calibre mould 47a being somewhat smaller in the region of the upper edge 52 than the diameter D2 of the upper edge 52. Sealing in the region of this upper edge 52 is thereby produced by the lip-shaped upper edge 52 of the stopper part 40 first produced, as is readily evident in Figs. 5a and 6.

This sealing can however also be achieved by appropriately shaping the cutting die (not shown) in the second working step (punching out the stopper parts 40 first produced), so that the first rubber sheet 46a is initially compressed somewhat before the punching step takes place. The punching step is then conducted with a diameter of commensurate size. After punching, the relative portion of the stopper part 40 first produced expands outwardly somewhat in a radial direction, so that the punched edge of the stopper part 40 first produced has a somewhat larger outer diameter D2 than the outer diameter of the bowl-like inert polymer foil 8.

If the stopper part 40 first produced is to obtain a larger axial expanse and the associated inert foil 8 is to be drawn particularly deep, the first counter-plate 42a of the first moulding tool may have a projection 53 through which a corresponding recess 54 is formed at the upper end face of the stopper part 40 first produced

(cf. Fig. 5b). With such an embodiment one can also enlarge the surface 55 which connects the stopper part 40 first produced to the second stopper part 43 to be produced afterwards, as is readily evident in Fig. 5b.

The second moulding tool 43 (Fig. 6) is then closed as a further working step. The material of the second rubber sheet 50 flows into the cavity 56 of the upper calibre 57 of the second moulding tool and a stopper as described similarly in connection with Figs. 1 and 2 is produced.

Fig. 7 shows a working step modified in comparison to the working step according to Fig. 6. There the lower calibre plate 49a of a second moulding tool 48a is altered in comparison to the embodiment of Fig. 6 as follows: The hollow calibre mould 47b of Fig. 7 has a concave bulge 59 radially exceeding the conical insertion part 13 of the stopper part 40a first produced. This stopper part 40a first produced, including its bowl-shaped, inert polymer film 6 or the like, is not yet finally shaped. As the mould 48a is closed, not only is the stopper part 43 to be produced in the last manufacturing stage formed, but sufficient pressure is built up in the lower calibre 49a in order to once again deform the already pre-formed stopper part 40a together with the inert polymer foil 3 or the like. One then obtains a stopper 2f (Fig. 8) having at its inner end a circumferential bulge 53 protruding somewhat radially in accordance with the shape of the concave bulge 59 in the lower calibre 49a. Such a stopper 2f can, for example, be fixed especially well in the neck of the bottle 1a.

Although the preferred field of application for the stoppers 2 produced according to the application is closures for medicine bottles or similar containers with pharmaceutical preparations,

these stoppers 2 and the method for producing them also lend themselves well to use in the field of receptacles with other highly sensitive contents.

Both the method of production, which according to the invention is subdivided into several working steps, and the stopper 2 have the following advantages among others: Since the stopper neck 4 is smaller in diameter than the outer part 5, which belongs to the stopper and radially protrudes beyond the stopper neck in a flange-like manner, and it is always only one part of the stopper neck 4 which is sheathed with fluorinated polymer film 3 or the like, one can manage with a relatively small amount of expensive polymer film 3 or the like. This may be of especial benefit for the method of production in several working steps. In the first working step with the first moulding tool 45, the calibre moulds 47 for the stopper parts 40 to be produced first or corresponding "groups" of moulds can be disposed closer to one another than if the entire stopper 2 were to be produced straight away together with the correspondingly large outer part 5 of the stopper. Accordingly considerably more parts 40 per unit of area can be produced per pressing operation in such a moulding tool 45. This permits a considerable saving in high-grade, very expensive foil material of fluorinated polymer or other chemically inert films 3a. The saving may potentially be up to 50% of that which would be necessary for producing stoppers in one piece if almost the entire underside thereof were coated.

The fluorinated polymer films 3a, as shown for example in Fig. 3, may be extruded, cast or peeled. It is appropriate for the thickness thereof to be between 0.01 and 0.5 mm.

As already partly indicated above, essential advantages of the stopper 2 according to the invention or of a similar seal consist in the following: Part of the stopper surface facing the sensitive contents of the container is not only surrounded by but also directly and inseparably connected to a fluorinated polymer film 3 or similar inert film. Between the fluorinated polymer film 3 or the like and the stopper portion of elastomeric material inseparably connected thereto there is virtually no joint, however narrow, capable of admitting impurities or the like. The fluorinated polymer film 3 or the like can assume a sealing function relative to the inside wall 7 or 100 of the container with respect to the contents 12 of the container in such a manner that to all intents and purposes the contents cannot react unwantedly with the remaining rubber elastic part, e.g. part 23 of the stopper 2d (Fig. 15) or the like. This is possible not only in the case of e.g. cylindrical stoppers or shaped stoppers of simple contours (e.g. Figs. 1 and 2), but also in the case of highly fissured stoppers such as freeze-drying stoppers (cf. Fig. 16). The area in which a fluorinated polymer film 3 or similar inert film covers the stopper 2 or the like may also be adapted to the various requirements (cf. Figs. 16 to 18). After the working step last described has been concluded, the stopper 2 or the like is punched out of its rubber sheet 50. An important aspect for the method according to the invention consists in that a fluorinated polymer foil 3a or similar foil consisting of inert material can be deep drawn in a manner which is very convenient, dependable and saves material, the material for the rubber-elastic part 23 of the stopper 2 or the like also forming, so to say, an elastic pad when the polymer film 3 is deep drawn. It is also of advantage that the fluorinated polymer foil 3 or the like is deep drawn in the same working stage as the production of the stopper part 40 first made. In addition, when the polymer foil 3 or the like is deep drawn at the same time as the stopper part 40 first made is produced, one can avoid unwanted shrinkage of polymer foils, this occurring as a rule when such polymer foils are deep drawn on their own. The method according to the invention largely ensures that this

inert film forms on the rubber-elastic stopper material a thin coating which is geometrically defined with sufficient accuracy.

In order to achieve a mechanical connection relative to the rubber-elastic part 23 of the stopper 2 or the like, a polymer foil 8 or the like is usually prepared in a chemical manner, the respective surface of the polymer foil 8 being made to afford a sufficiently good "grip" so that - seen in the micro range - the material of the rubber-elastic part 23 can connect firmly to the polymer foil 8 during vulcanization in a mechanical manner by interhooking or interlocking etc.

Fig. 8 also shows a known flanged cap designated by 61, with which it is achieved that the underside 15 of the stopper top 5 is pressed sufficiently firmly onto the end face 10 of the container opening 3.

Stoppers, as were described above and shown by way of example in Figs. 1 and 2, have proved good in testing if they are pierced only once.

However it has proved that such stoppers, which in principle are of great advantage, may have drawbacks in certain uses, if, for example, they have to be pierced twice. Fig. 9 shows, for example, a stopper 2 similar to that in Fig. 1, the stopper neck 4 thereof being sheathed with a polymer film 8 in a portion facing the interior 6 of the bottle. If one inserts an infusion prick 60 into such a stopper 2, the infusion prick deforms the polymer film 8 at the puncture point. The polymer film 8 or the like bends in the direction of the interior 6 of the container, while forming a puncture slit. When one removes the infusion prick 60, as evident in Fig. 10, the fluorinated polymer film

8 or the like retains approximately the shape assumed after piercing of the infusion prick 60.

Fig. 10 also shows the slit 63 formed in the polymer film 8 at the point earlier punctured by the infusion prick 60. The polymer layer 8, which is firmly connected to the rubber-elastic material of the stopper neck 4 also in the region of the puncture point, can then keep this rubber-elastic puncture point 63 open a little, at least in areas, essentially in the neighbouring region of the polymer film 8. This has to do with the fact that the fluorinated polymer film 8 or the like has been greatly stretched by the production process described above and strives to return to its original shape (memory effect). Now if, after an infusion prick 60 has punctured the stopper 2 for the first time and has been removed, e.g. mixing movements are performed with the preparation or the preparation develops gas pressure when dissolving, the behaviour of the fluorinated polymer film 8 or the like may in such cases have negative consequences. This is because the polymer film 8 or the like, which is ruptured in a slit-like manner and is deformed, keeps the rubber puncture point 63 open a little. Liquid or part of the medicament may pass out through the puncture point 63 during shaking or through excess pressure. This may be a drawback in several respects. For example, dosage of the medicament is no longer reliable. The contents of the bottle may also have an unwanted chemical effect on the person handling it.

In order to avoid the drawbacks last described occurring in special cases, the invention is developed further as follows: The connecting surface 62 (Figs. 11a, 11b) with which the fluorinated polymer film 8 enters into a bond with the stopper neck 4 is either not made adhesive at all or - as preferably occurs in practice - is

made incapable of adhesion in the region of the puncture point 63 for the infusion prick 60. For the inert film 8 preferably consisting of PTFE is normally first made to be adhesive by etching what is later its connecting surface 62, etching making a suitable surface structure possible. In the exemplified embodiment according to Figs. 11a, 11b, the surface structure caused by etching is neutralized, preferably by means of heating the puncture point 63 of the polymer film 8. Then the PTFE foil 8 does not connect to the rubber-elastic material of the stopper neck 4 in this region. The special configuration of the inert film at the puncture point 63 is indicated in Figs. 11 and 12 by the solid black line in region 63. As for the rest, a first stopper part 40 with an inter-rupted connecting surface at the puncture point 63 is produced - as indicated in Fig. 12 - similarly to that described above, particularly in connection with Fig. 6.

Such a desired interruption of the connecting surface 62 at the puncture point 63 can be achieved not only in that - as described above - the inert film 8 has its surface structure caused by etching neutralized by heat. The fluorinated polymer film 8a located in a bandlike manner above the moulding plate 41 (Fig. 13) can for example be treated by adding chemicals to the subsequent puncture point 63 in such a way that no connection is established between the rubber-elastic material of the stopper neck 4 on the one hand and the connecting surface 62 of the polymer film 8a on the other hand when the first stopper part 40 is produced.

For this purpose in Fig. 13 e.g. spatially exactly defined portions 64 of a chemical are applied which prevents adhesion unwanted there of the inert film 8, 8a in the production process. As for

the rest, the production process according to Figs. 13 and 14 corresponds essentially to the production process which was already described in connection with Figs. 3,4,6 and 7 and was explained more closely above.

In a stopper 2, the lower part 40a of which (Figs. 11a, 11b) is produced according to the method described in connection with Figs. 9 to 14, the fluorinated polymer film 8 or similar inert film is deformed as the infusion prick 60 penetrates this stopper part 40a in the same way as was described in connection with Figs. 9 and 10. This also has to do with the fact that the inert film usually consisting of PTFE is not permanently deformed at temperatures which rubber or rubber-like material tolerates. Accordingly there is the problem in the production process according to the invention that PTFE or the like is deformed in connection with the rubber under the moulding plate 41, but stress towards reassuming the old shape of the inert film 8a remains. As the infusion prick 60 is withdrawn according to Fig. 10, parts of the polymer film 3 also remain in the deformed position in the puncture area 63, as schematically indicated in Fig. 10. If, however, there is no connection at this puncture point 63 between the polymer film 8 or the like on the one hand and the rubberlike material of the stopper 2 on the other hand, the stopper neck 4 can close again in the usual manner after removal of the infusion prick 60. One can then safely shake the contents of the bottle, as is advisable e.g. for the reconstitution of freeze-dried products. By "reconstitution" one understands here that such a product is dissolved again by adding liquid. Even should excess pressure arise in the interior 6 of the bottle in adding a liquid or a constituent of a medicament and/or in shaking, one still obtains a sufficiently

dependable closure of the medicine bottle 1.

Through the various working steps it is also possible for multi-layer stoppers, e.g. ones in three layers, to be produced with the aid of the method according to the invention. Through being composed of three layers these further optimize the properties of the material in the individual stopper areas. Thus Fig. 15 shows a modified exemplified embodiment of the stopper described hitherto: There, in the rubber-elastic part 23 of the stopper 2e, the stopper neck 4 consists of a different rubber-elastic material than the outer part 5 of the stopper, this being indicated by different hatching. It is thereby possible to optimize the desired properties of the material in the two different rubber-elastic parts 33 and 39. For example, in the case of the material for the part adjacent to the fluorinated polymer film 8, one can use rubber material which lends itself particularly well to entering into a connection with the polymer film 8. One can select the rubber material later forming the outer part 5 of the stopper e.g. from the viewpoint of good sealing ability, e.g. after an infusion prick 60 has been removed, or from the viewpoints of connectability to the lower part of the stopper, or of price.

Fig. 16 shows a further modification of a shaped stopper 2d, which has an outer contour usual for freeze-drying stoppers. Here the stopper neck 4 has an outer, cylindrical sealing piece 29. An inner end 30 is adjoined thereto in the direction of the interior 6 of the container. Recesses 31 which are open at the edge and in cross section are usually in the shape of a sector of a circle and a central blind hole 32 are formed in the inner end. The entire inner end 30 of this freeze-drying stopper 2d

is coated with a continuous fluorinated polymer film 8. This polymer film 8 extends into the lower attachment area of the cylindrical sealing piece 29, so that the contents 12 of the container are protected against direct contact with the rubber-elastic part 23 of the stopper 2d. After the stopper 2d has been completely pressed into the container opening 3, dependable sealing of the cylindrical sealing piece 29 is nevertheless produced by means of its portion consisting of rubber-elastic material.

The method according to the invention can be implemented to advantage not only in producing the stoppers already described above, but also e.g. for producing closure elements, pistons or similar seals, as becomes clear from Fig. 17.

Fig. 17 shows as a modified example of use a twin-chamber hypodermic ampoule designated altogether by 15. It is closed at its rear end by a piston stopper 17 and the interior 18 of the barrel of the ampoule is subdivided into two portions 20 and 21 by a separating piston 19. The medicine bottle 1 of Fig. 2 and the barrel 22 of the syringe are here jointly designated as "containers".

Sensitive pharmaceutical preparations may also be located in the portions 20 and/or 21 of the barrel 22 of the syringe. The piston stopper 17 and/or the separating piston 19 may then take a form similar to the stoppers 2, 2a already described and have on one or also on both of their end faces a fluorinated polymer film 37 (cf. Fig. 18).

As per a further development according to the invention, the piston parts 19, 19' in Fig. 17 are produced separately and

interconnected by a coupling piece 70. Consequently the two inert films 8 are external.

Fig. 13 shows a piston 33 similar to the separating piston 19 and piston stopper 17, as already described in Fig. 17. The piston has three radially protruding sealing bulges 34, 35 or 36 or similar sealing lips. The sealing bulge 34 closest to a pharmaceutical preparation and the respective end face 37 of this piston 33 are sheathed with a fluorinated polymer film 8 which according to the invention is undetachably connected to the rubber-elastic material of the piston 33.

Using the cylindrical or at least essentially cylindrical stopper neck 4 of the stopper 2 according to the invention or the like, according to Figs. 1 to 13, one can achieve sealing of the interior 6 of the container inside a cylindrical or at least essentially cylindrical container opening, i.e. without recourse to the end face which belongs to a flange at the opening of a container 1 and may be problematic in its sealing efficiency. In such a stopper neck 4 or the like, two different materials bring their advantageous properties into effect without it being possible for the same to be negated through impurities conditioned by production or through one layer of the stopper becoming unintentionally detached. The fluorinated polymer film 8 or similar inert film separates the contents of the bottle - particularly during the time it is in storage - from the rubber-elastic part of the stopper 2. This rubber-elastic part of the stopper neck 4, in contradistinction, provides dependable sealing in the region of the at least essentially cylindrical stopper neck 4 and in so doing undertakes sealing functions which the fluorinated polymer film or the like is

incapable of performing.

In Figs. 16 to 18, those stopper parts averted from the interior of the respective containers, e.g. ampoule chambers 20 and 21 of the hypodermic ampoule 16, are designated by 5'.

Patent Claims

1. A method for producing a pharmaceutical stopper, piston or similar seal (2 - 2f) which consists essentially of rubber or a similar elastomeric material and serves to close or subdivide a bottle (1), a barrel (22) of a syringe, or a similar container, the stopper, piston or the like having in a sealing area facing the interior (6) of the container a coating of a fluorinated polymer film (8) or similar inert film only partly surrounding said sealing area of the stopper at the side thereof facing the wall of the container opening, so that a further part of the uncoated sealing area of the stopper sealingly butts against the container opening (3), characterized in that the stopper or the like is produced in several working steps, in the first step an unvulcanized rubber sheet (46) together with a fluorinated polymer film or similar inert film (8) is initially pressed into a calibre plate (41) of a first moulding tool (45) and then corresponding portions of the polymer film or the like (8) and of the rubber sheet (46) assume the outer contour corresponding to the hollow mould(s) (47) provided in the calibre plate (41), polymer film or the like (8) resting against the wall of the hollow mould (47) being inseparably connected under the influence of heat to the part of the rubber sheet (46) lying within and being vulcanized to form in each case one inner sealing part (46a) of the stopper (2), that in the next working step the

inner sealing parts (46a) of the stopper (2) which have thus been formed and are coated with the fluorinated polymer or the like (8) are removed from the first moulding tool (45) and in the next working step are punched out of the coated rubber sheet (46) in such a manner that the upper edge (52) of each inner rubber sealing part (46a) protrudes somewhat radially with a diameter (D 2) beyond the diameter (D 1) given by the hollow mould (47), that in the next working step in which the inner sealing part (46a) is placed in the hollow mould(s) (47a) of a second moulding tool (48, 48a) said protruding upper edge (52) upwardly (at 51) seals said hollow mould(s) in such a way as to prevent that in the next working step, when the inner sealing part (46a) is joined to an outer part (5) of the stopper, unvulcanized rubber material of the subsequent outer part of the stopper enters the area between fluorinated polymer film or the like (8) and the wall of the hollow mould (47a, 47b) of the second moulding tool (48, 48a).

2. The method as claimed in claim 1, characterized in that an unvulcanized rubber sheet or similar caoutchouc plate is connected to a fluorinated polymer film or the like (8), possibly with the use of adhesive agents, appropriately by rolling on.
3. The method as claimed in claim 1 or claim 2, characterized in that the fluorinated polymer film or the like (8) and the unvulcanized rubber sheet (46) or similar caoutchouc plate are interconnected before they are placed between the counter-plate (42) and the moulding plate (41) of the first moulding tool (45).

4. The method as claimed in any one of claims 1 to 3, characterized in that the closing operation of the first moulding tool (45) in the first working step is controlled in such a way that as the pressure slowly rises the unvulcanized rubber sheet (46) or similar caoutchouc plate penetrates into the hollow mould(s) (47) of the first moulding tool (45) and deep draws the fluorinated polymer film or the like (8) so as to be free from cracks and folds, the corresponding portions of the unvulcanized rubber sheet (46) or the like acting as a pressure pad.
5. The method as claimed in any one of claims 1 to 4, characterized in that the fluorinated polymer film (3) or the like serving to coat the stopper (2) or the like has a thickness of between 0.01 and 0.5 millimetres.
6. The method as claimed in any one of claims 1 to 5, characterized in that the inner sealing part (46a) belonging to the stopper or the like (2) and produced in the first working step initially remains still deformable and undergoes further deformation inside the second moulding tool (48), a bulge (58) being formed which preferably projects somewhat radially beyond the remaining diameter (D_1) of the sealing part.
7. The method as claimed in any one of claims 1 to 6, characterized in that for the outer part (5) of the stopper a different rubber material is used than the inner sealing part (46a) belonging to the stopper or the like (2 - 2f) and bearing the fluorinated polymer film or the like (8).

8. The method as claimed in any one of claims 1 to 7, characterized in that the adhesion of the fluorinated polymer film or the like (8) relative to the inner sealing part (46a) or the like is counteracted by producing an inert state in prescribed areas - e.g. the puncture point (63) - before the connection of polymer film or the like and inner sealing part or the like.
9. The method as claimed in claim 8, characterized in that the inert state is produced by punctual application of a chemical checking adhesion on the fluorinated polymer film or the like (8) or by neutralizing etching of the foil, preferably by means of a short, punctual application of a temperature between 250° and 400°C, preferably between 300° and 320°C.
10. A pharmaceutical stopper (2 to 2f), piston (17, 33) or similar rubber seal for closing or subdividing a bottle (1), a barrel (16) of a syringe, or a similar container, the stopper or the like being partly coated with and inseparably connected by vulcanization to a fluorinated polymer film or the like on a stopper area facing the interior (6) of the container, only one portion (30, 34) of the stopper shaft or the like being covered by the fluorinated polymer film (8) or the like and a further part (14; 29) of the essentially cylindrical sealing portion as well as a stopper part (5, 5') averted from the interior (6; 20, 21) of the container having a sealing face free of coating.
11. The pharmaceutical stopper, piston or the like as claimed in claim 10, characterized in that the stopper or the like (2-2f) is composed of three layers, the first layer facing the interior of the container consisting of the fluorinated

polymer film (3) or the like and being inseparably connected by vulcanization to a second layer of rubber or similar elastomeric material and said layer extending at least to the height of the fluorinated polymer film or the like (3), and that a third layer of rubber or similar elastomeric material is adjoined thereto, said third layer forming an outer end (43) of the stopper and being firmly connected to the second layer (40) by direct rubber to rubber connection.

12. The stopper or the like as claimed in claim 10 or claim 11, characterized in that the layer thereof consisting of rubber or rubber-elastic material (40) and facing the interior of the container has directly at the outer edge of the associated fluorinated polymer film or the like (3) a lip-shaped sealing edge (52), the outer diameter (D 2) thereof being somewhat larger than the outer diameter (D 1) of the area sheathed by fluorinated polymer film.
13. The pharmaceutical stopper, piston or the like as claimed in any one of claims 10 to 12, characterized in that the insertion part thereof takes the form of a freeze-drying stopper (2 d) consisting of an uncoated, cylindrical sealing part (29) with an end (30) which adjoins in the direction of the interior of the container and has openings (31), the inner contour of said end being completely coated with a fluorinated polymer film or the like (3) and the outer contour of said end being coated therewith up to the height of the cylindrical sealing part (29).
14. The pharmaceutical stopper, piston or the like as claimed in any one of claims 10 to 12, characterized by taking the form of a piston (33) with two or more radial sealing bulges

(34, 35, 36), preferably only one of the sealing bulges (34) being covered with a fluorinated polymer film or the like (8).

15. The pharmaceutical stopper, piston or the like as claimed in claim 14, characterized by taking the form of a two-part piston or the like (17, 19) preferably connected by means of a coupling piece (70), possibly each part having one or more radial sealing bulges (34, 35, 36) of which in each case one (34, 36) is coated with a fluorinated polymer film or the like (8).
16. The pharmaceutical stopper, piston or the like as claimed in any one of claims 10 to 15, characterized in that the part which is coated with a fluorinated polymer film or the like (3) and belongs to the inner end of the stopper or the like (2 f) has a bulge (58) protruding radially beyond the diameter of the uncoated part of the stopper shaft.
17. The pharmaceutical stopper, piston or the like as claimed in any one of claims 10 to 16, characterized in that the rubber-elastic parts (38, 39) thereof consist of two different rubber materials.

1/6 M 18-08-86

Fig. 1

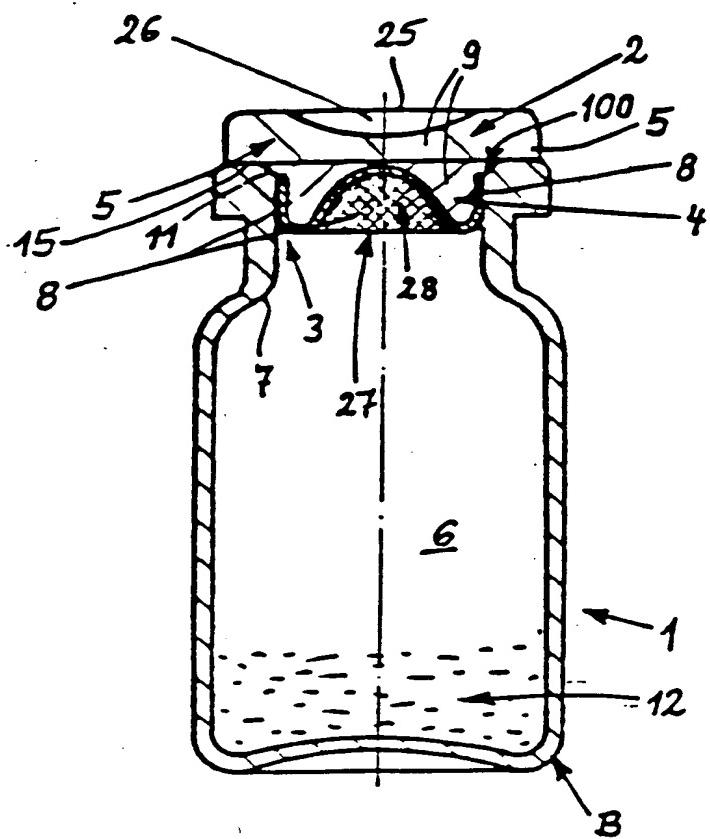
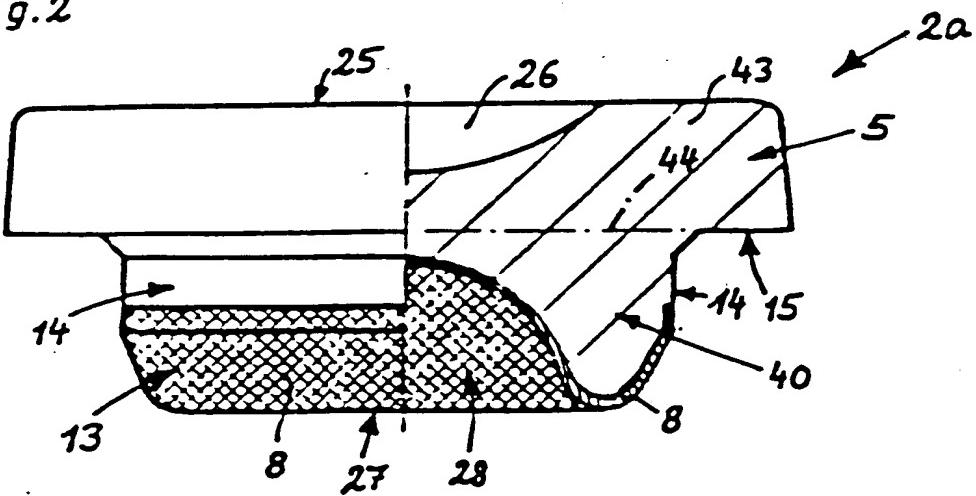


Fig. 2



2/6 M 10·08·08

Fig. 3

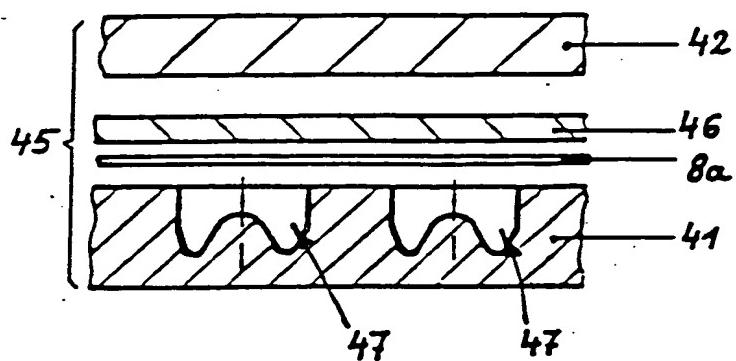


Fig. 4

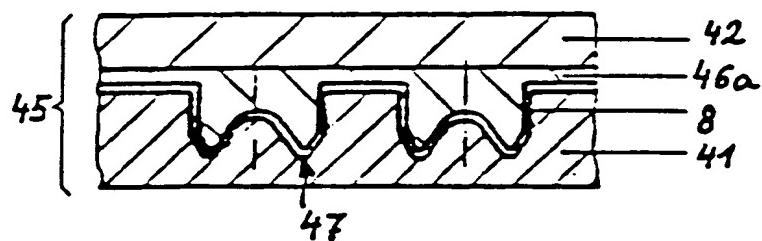


Fig. 5a

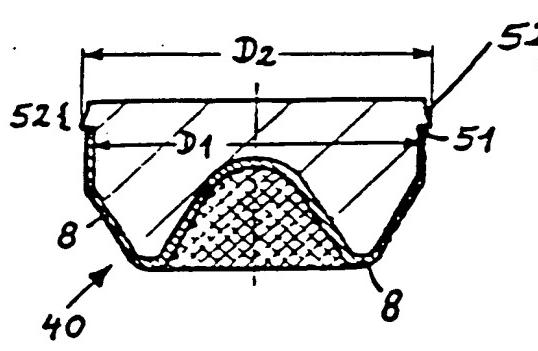
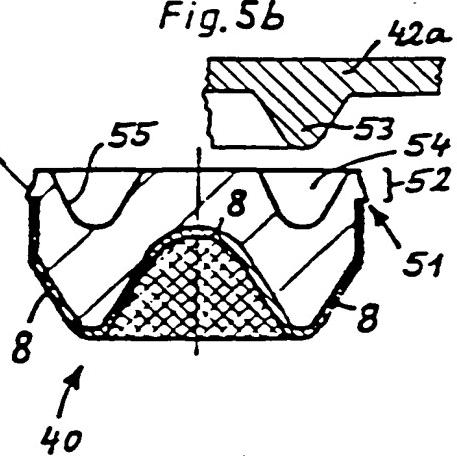


Fig. 5b



3/6

M 18-08-68

Fig. 6

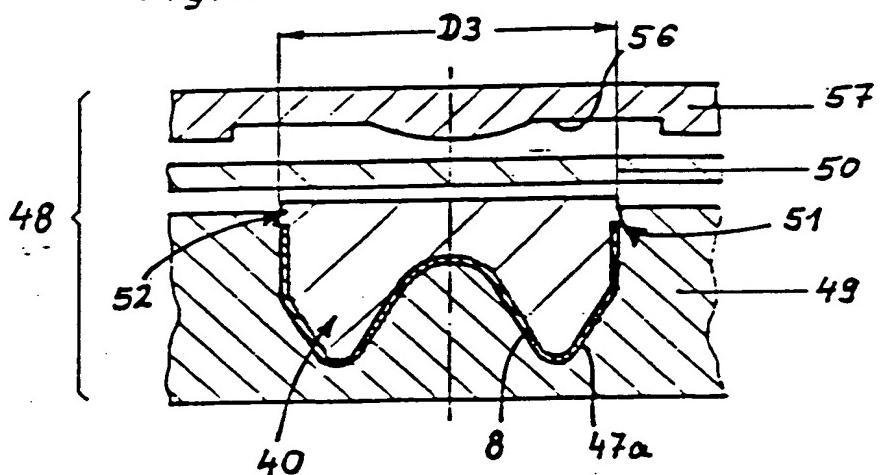


Fig. 7

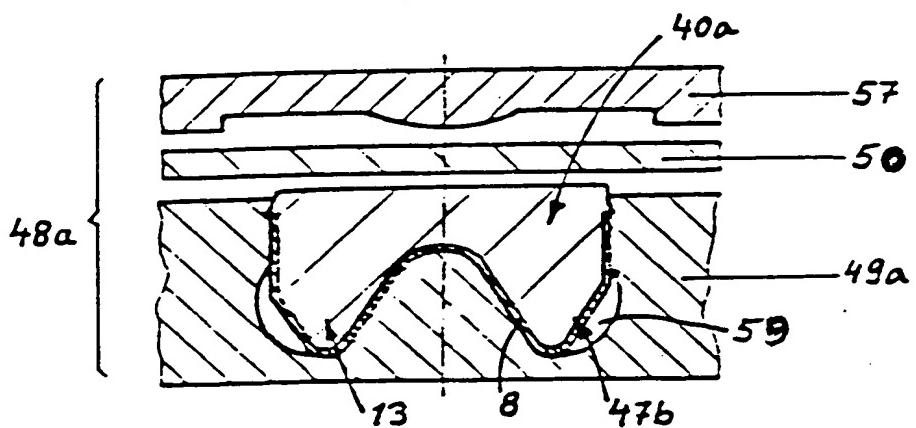


Fig. 9

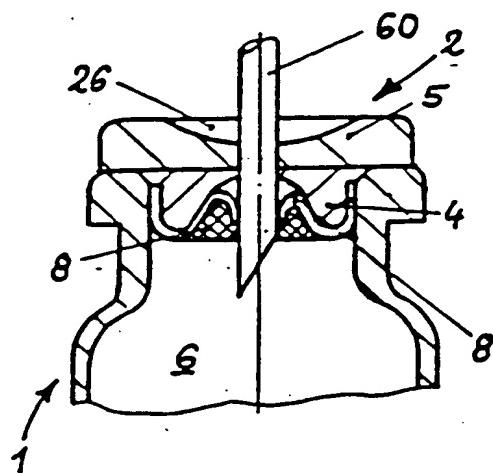
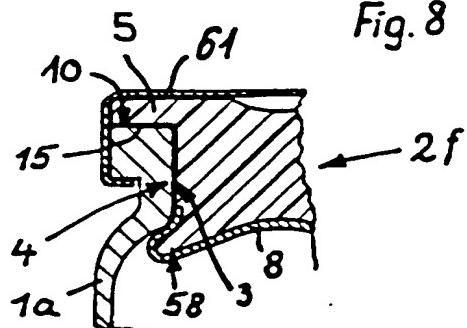


Fig. 8



4/6

M 18-08-88

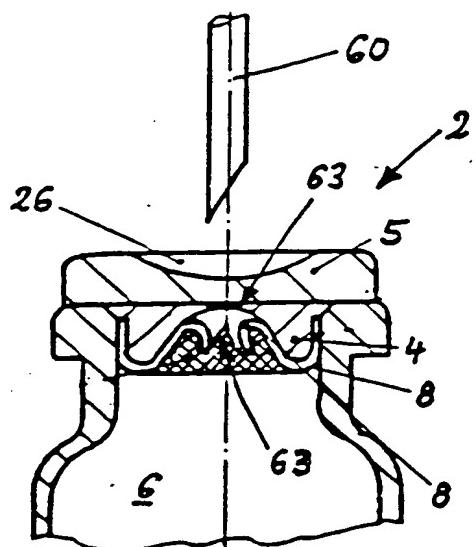


Fig. 10

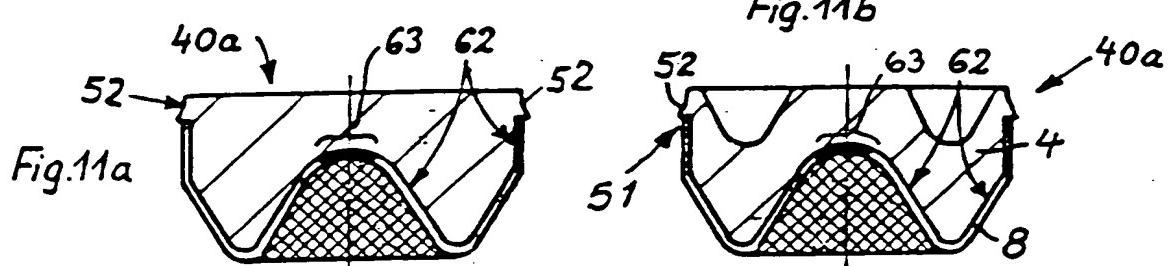


Fig. 11a

Fig. 11b

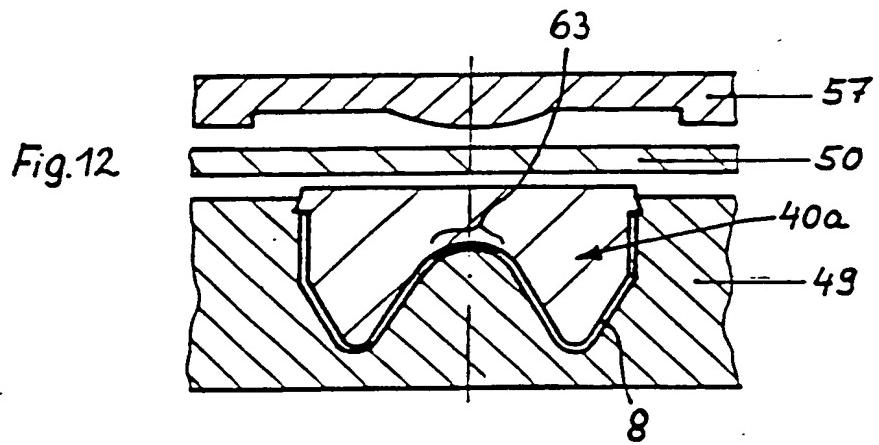


Fig. 12

5/6

M 10-08-88

Fig. 13

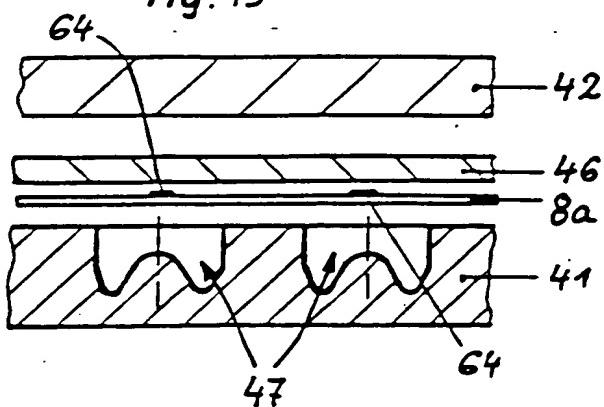


Fig. 14

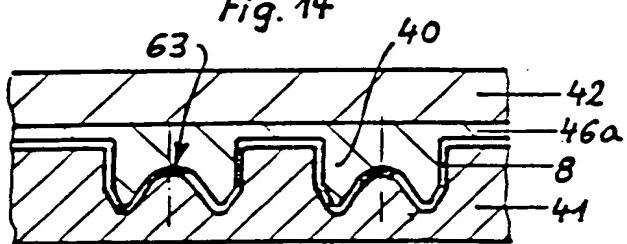
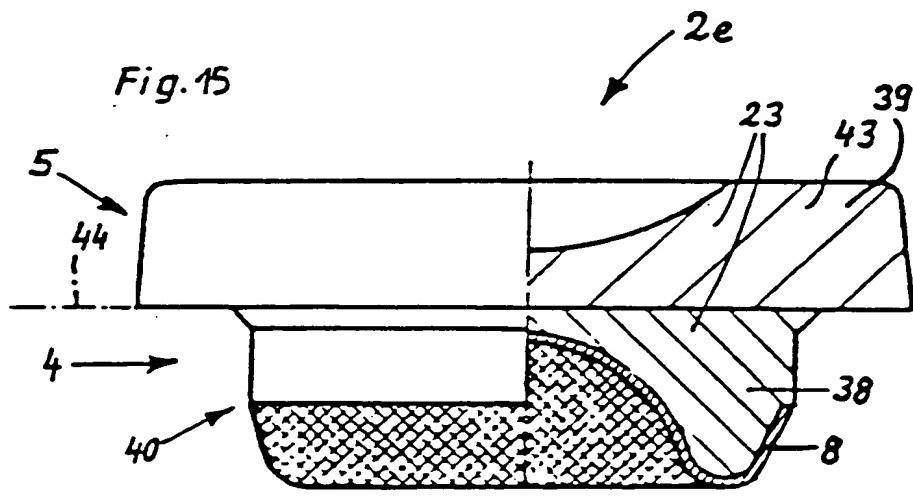


Fig. 15



6/6 M 18-08-68

Fig. 16

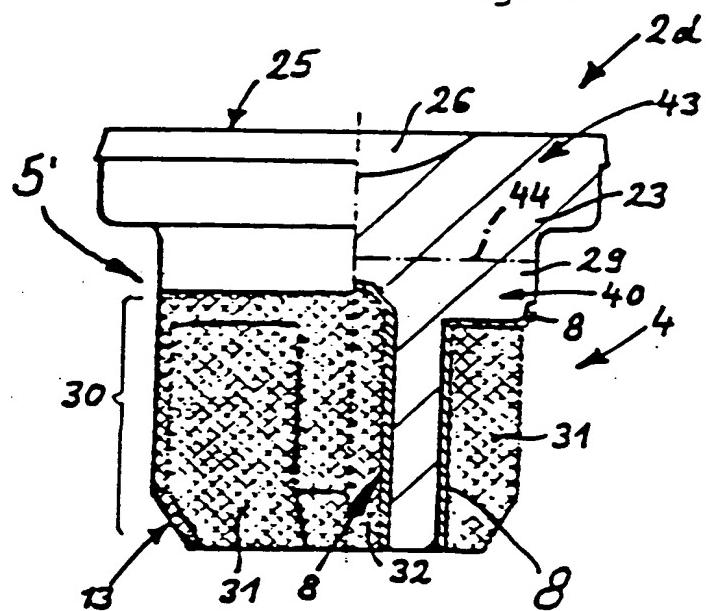


Fig. 17

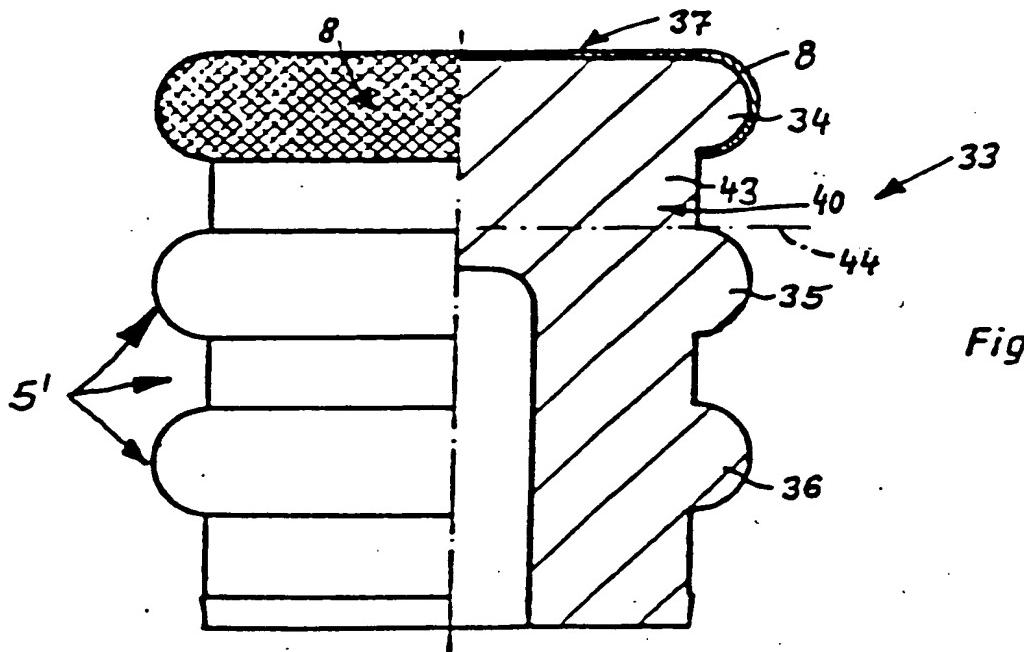
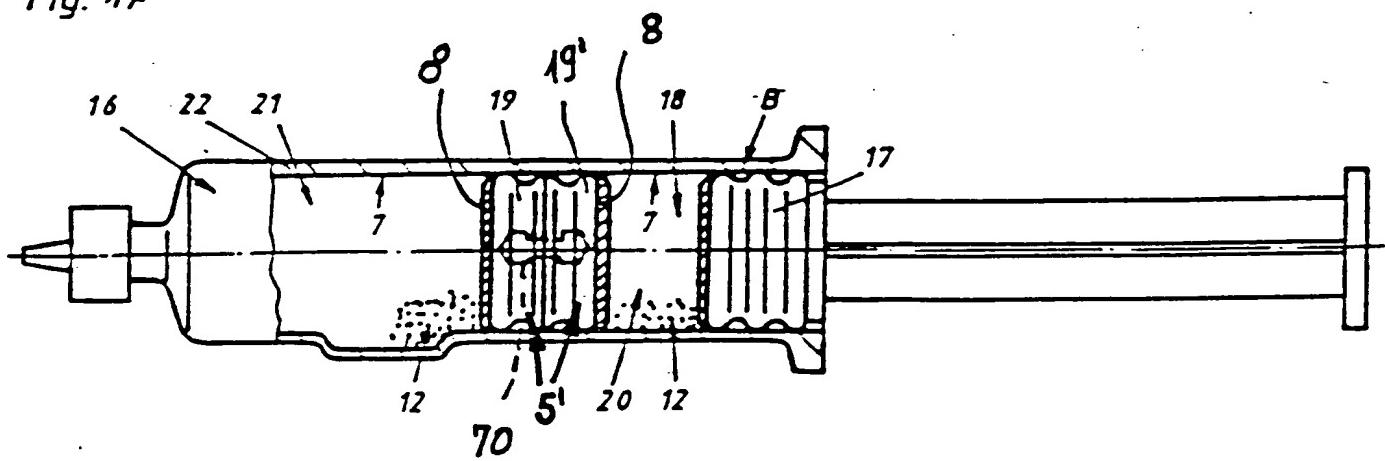


Fig. 18